Remarks

Applicants will address the Examiner's remarks in the order presented by the Examiner in the Office Action mailed August 28, 2002.

Drawings

The Examiner has requested revised drawings for figures 6 and 10 and these are provided herewith.

Claim Objections

Claim 11 is objected to because of the phrase "a chemotherapeutic or an immunosuppressive." The Examiner has suggested that Applicants add the term "agent," which Applicants have done. Thus, the objection should be moot.

Claim Rejections-35 USC Section 112,First Paragraph

Claims 10 and 11 stand rejected under Section 112, first paragraph, because the Examiner believes that Applicants' invention is enabled for direct administration to a tumor, and not as now broadly claimed. Applicants submit that based on the type of tumor a patient has, different modes of administration will be practiced by a skilled practitioner of this art. For instance, in those instances where the tumor is confined, an example being a brain tumor, Applicants' methods will be beneficially applied by contacting the exterior of the tumor with their adenoviral vectors. This can be achieved by direct injection of the adenoviral vectors into the cranical cavity. Another example is liver cancer. Here the adenoviral vectors can be, indeed have been, administered by intraarterial injection so as to cause the adenoviral vectors to come in contact with, and kill the tumor. To support this statement, Applicants are providing herewith copies of two publications by Reid et al. (Cancer Research: 62, 6070-6079, 2002; and, Gene Therapy: 8, 1618-1626, 2001) which clearly show that an adenovirus has been administered by hepatic-arterial infusion, and that this mode of administration yields anti-tumor activity. Lastly, in the case of certain solid tumors, they may be best treated by direct injection of the adenoviral vectors into the tumor. This method is well known and widely used.

It will be appreciated that all of these methods have been utilized by skilled practitioners of this art to treat cancer. Applicants have thus amended the claims to recite claiming a method that involves "...directly treating a mammal's neoplastic condition..."

Applicants respectfully submit that this amendment to the claims should obviate the rejection.

The Examiner has indicated that Applicants' methods/adenoviral vectors are enabled for administering anti-tumor genes in a method of treating a mammal having a tumor, but that it is not apparent to one skilled in the art how to use any heterologous gene for such treatment. Applicants have amended claims 1 and 15 to recite that the heterologous gene encodes a protein that has anti-tumor activity. Thus, this amendment should obviate this aspect of the rejection.

Claim Rejections-35 USC Section 112, Second Paragraph

Claims 2-6 and 11 stand rejected under section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner has stated that the use of "An" in the claims renders them indefinite because it does not point out which composition an adenoviral vector is referring to in the claim. As suggested by the Examiner, Applicants have amended claims 2, 3, 4, and 6 to delete "An" and substitute in its place "The."

The Examiner has similarly rejected claim 11, and Applicants have amended it accordingly.

With regard to claim 6, Applicants note that it is an independent claim, and thus does not suffer the same indefiniteness, and thus no amendment is required.

The Examiner has also rejected claims 3-5 under section 112, second paragraph, as being incomplete. Specifically, the Examiner has stated that the claims should recite certain structural elements, and has suggested an amendment to obviate the rejection. Applicants believe that the Examiner is asking that the "E1b gene deletion" refer to "genes" that are deleted, and not to proteins encoded by the genes. Applicants have amended the claims as suggested. Applicants have made a similar amendment to claim 2, which was not part of the rejection.

Claim Rejections-35 USC Section 102

Claims 1-3, 6, 7, 9-11 and 14-15 stand rejected under 102(e) as being anticipated by Bischoff (US Patent No. 6, 080, 578). The Examiner has stated that Bischoff et al.

teach Applicants' recombinant adenovirus constructs. Applicants respectfully disagree for the following reasons.

First, Bischoff et al teach adenovirus constructs that have a "...deletion or point mutation, in the E1a and/or E1b gene regions, especially in the sequences encoding the E1b p55k protein..." (Column 4, lines37-39). This is distinct from Applicants' invention which involves the deletion of *large* stretches of nucleotides from the E1b region. Indeed, in some embodiments the entire E1b region is deleted, not just the region, or that part of the region that encodes the p53 binding protein, p55.

Bischoff et al's invention is the use of adenoviral vectors that have the E1b region that encodes the p53 binding protein, p55, altered, or not expressed, so that it does not bind p53. Hence, the selective killing of p53 negative tumor cells. Any mutation, including deletions, frameshifts, etc., are made to achieve this result. Applicants' adenoviral vectors, on the other hand, are quite distinct in that they do not rely on a mutation in the E1b 55K region to produce an altered p55 that does not bind p53. Applicants claim adenoviral vectors having certain E1b region genes removed. In one embodiment, Applicants claim deleting E1b55K, but it is in the context of other E1b genes deleted with the 55K gene. And, these constructs of the Applicants have the further property, as now claimed, of having an anti-cancer gene under the control of the E1b promoter. None of these features of Applicants' adenoviral constructs are explicitly shown by Bischoff et al., which is required if a reference is to be used to support a 102 rejection. Hence, Bischoff cannot sustain a 102(e) rejection, and Applicants respectfully request that the rejection be withdrawn.

Second, in column 3, lines 54-65, Bischoff et al., state:

"In preferred variations of these embodiments, the recombinant adenovirus comprises an E1b locus encoding a mutant p55 which is substantially incapable of binding p53 and may optionally also lack a functional p19 protein (i.e., incapable of inhibiting expression of adenoviral early region genes in the presence of E1a polypeptides). Recombinant adenoviruses of the invention may further comprise a mutant p19 gene which produces enhanced cytopathic effects; such a mutant known in the art is the p19 cyt mutant gene. However, it may be preferable to retain functional p19 in some mutants to maintain the integrity of viral DNA during the infection."

Here, Bischoff et al. describe an adenoviral vector that has the E1b region that codes for 55K mutated so that p55 cannot bind p53, AND optionally lacking a functional

p19 protein. The point Applicants wish to make is that in the context of more than one gene in the E1b region being deleted, Bischoff et al. do not state that the gene that codes for p19 should be deleted. This is yet another reason why Bischoff et al cannot support a 102(e) rejection.

Third, in column 4, lines 51-55, Bischoff et al. state:

"In some embodiments, a negative selectable gene, such as an HSV tk gene, is operably linked to an early region (e.g., E2, E1a, E1b) enhancer/promoter, a late region gene enhancer/promoter (e.g., major late promoter), or an early or late region promoter with a CMV enhancer, in a recombinant adenovirus construct also comprising an E1a or E1b mutation, so that the negative selectable gene is preferentially transcribed in infected cells which express a replication phenotype (i.e., neoplastic cells) and provides negative selection of such cells by administration of an effective dosage of a negative selection agent (e.g., gancyclovir, FIAU). A negative selectable gene may be inserted in place of an E1a and/or E1b structural sequence to concomitantly form an E1a.sup.(-) replication deficient mutant, E1b.sup.(-) replication deficient mutant, or E1a/E1b double mutant, respectively."

It will be appreciated that all of the adenoviral constructs envisioned in this description require a mutation, however defined, in the E1b 55K gene to yield p55 that cannot be expressed, or if expressed, cannot bind p53. Such constructs can have a "negative selection gene" driven off of the E1b promoter, BUT such constructs are not stated to have deleted other E1b genes. Thus, Applicants submit that this is another reason why Bischoff et al. is an improper 102(e) reference.

Finally, Applicants draw the Examiner's attention to pages 13 and 15 of the Office Action mailed August 28, 2002, paper number 7. On page 13, the last sentence of the first full paragraph states:

"However, Bischoff does not specifically the production of a recombinant adenovirus vector comprising a deletion of E1b region gene, but retaining the E1b promoter, and substituting for said deleted E1b region gene, an anti-tumor gene, wherein the gene is cytosine deaminase (CD)."

On page 15, the first full sentence states:

"However, Bischoff does not specifically the production of a recombinant adenovirus vector comprising a deletion of E1b region gene, but retaining the E1b promoter, wherein the E1B gene deletion comprises pIX and substituting for said deleted E1b region gene an anti-neoplastic gene."

Both of these statements support Applicants' position that Bischoff et al. do not show each and every feature of Applicants' claims.

Based on all the above discussion, Applicants respectfully request that the 102(e) rejection be withdrawn.

Claim Rejections-35 USC Section 103

Claims 1, 5-13, and 15 stand rejected under 103(a) as being unpatentable over Bischoff (US Patent No. 6, 080, 578) taken with Garcia-Sanchez et al (Blood, vol. 92, 1998, pp. 672-682). For all the reasons presented above, and that are incorporated by reference herein, it is submitted that Bischoff et al. do not show or suggest Applicants' invention, nor does it provide any motivation to make the invention adenoviral vectors.

The secondary reference shows a replication incompetent adenoviral vector that has a "*portion* of the E1a and E1b gene region...replaced by the bacterial cytosine deaminase gene under the transcriptional control of the human CMV promoter..." (emphasis added, page 673, right column, last paragraph, second sentence). As discussed above with regard to the Bischoff et al. reference, Garcia-Sanchez et al. neither shows nor suggests any of the elements of Applicants' invention adenoviral vectors. For example, there is no showing or suggestion of any gene deleted from the E1b region.

Moreover, *AND, importantly,* there is no showing or suggestion of using the E1b promoter to drive an anti-tumor gene, whether the gene be thymidine kinase or cytosine deaminase. Rather Garcia-Sanchez et al. use the CMV promoter, essentially a constitutive promoter, such that the expression of cytosine deaminase occurs independently of those factors that control the expression of cytosine deaminase in Applicants' adenoviral vectors. Recall that a property of Applicants' adenoviral vectors is that the expression of an anti-tumor gene occurs in a temporal manner that is similar to the E1b region gene that it is substituted for. Considering this significant difference between Applicants' adenoviral vectors and those described by Garcia-Sanchez et al. it is not seen that a skilled practitioner of this art would be motivated to make Applicants' invention in combination with the Bischoff et al reference.

Thus, Applicants respectfully submit that neither Bischoff et al., nor Gracia-Sanchez et al. show or suggest Applicants' invention, nor do the references, alone or in combination, provide the motivation to make their invention.

Claims 1, 2, 4, 7, 14, and 15 stand rejected under 103(a) as being unpatentable over Bischoff (US Patent No. 6,080, 578) taken with Amalfitano et al. (US Patent No. 6, 328, 958, effective filing date 8/28/98). The Examiner's position is that while "Bischoff does not specifically the production of a recombinant adenovirus vector comprising a deletion of E1b region gene, but retaining the E1b promoter, wherein the E1B gene deletion comprises pIX and substituting for said deleted E1b region gene an anti-neoplastic gene" that it "...would have been prima facie obvious to a person of ordinary skill in the art ...to modify the recombiant adenoviral vector taught by Bischoff by deleting the pIX gene." Applicants respectfully disagree.

For reasons already presented above, and incorporated herein by reference, Bischoff et al. do not show or suggest many features of Applicants' invention, and thus does not render their invention obvious. Further, it is not seen that Amalfitano et al. provide any showing or suggestion of Applicants' invention, nor the motivation to make it in the context of adenoviral vectors having the pIX gene deleted for the following reasons.

First, note that Amalfitano et al. do not describe deletions in the E1b region that retain the E1b promoter so that it can be used to drive the expression of an anti-cancer gene.

Second, there is no description of adenoviral vectors with the properties of Applicants' adenoviral vectors that have the pIX gene deleted. Indeed, the only reference to pIX in Amalfitano et al. is in column 10, lines 39-41, where it is stated that: "In addition, deletions in the E4, E2a, protein IX, and fiber protein regions have been described..." Applicants respectfully submit that this statement alone does not provide the motivation to make Applicants' invention. There is, after all, no mention of how such constructs would be made or their properties; specifically, is the entire gene removed, or part of the gene? Is the protein IX gene being deleted with ONLY E1b genes, or with other genes? It would seem that deletions throughout the adenviral genome are contemplated.

Clearly, based on all the discussion above, Bischoff et al. do not show or suggest Applicants' invention, and it is not seen that Amalfitano et al. provide the motivation to make Applicants' adenoviral vectors with a deletion in the pIX gene. Applicants respectfully request that the rejection be withdrawn.

Comments

The Examiner will note that Applicants have amended claim 1 to better clarify what Applicants are claiming.

If the Examiner believes that an interview would expedite the prosecution of Applicants' patent application, the Examiner is encouraged to call the undersigned.

The Commissioner is authorized to charge any fees associated with this communication to Deposit Account No. 15-0615 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: February 28, 2003

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Appendix
Amended Claims
(version with markings to show changes made)

1. (Amended) A recombinant adenoviral vector comprising a deletion of at least one E1b region [gene(s)] gene, but retaining the E1b promoter, and substituting for said E1b [region(s) gene(s)] region gene a heterologous gene that [essentially exhibits the] has a similar temporal expression pattern of the deleted E1b region [gene(s)] gene, and said heterologous [gene(s)] gene having the further property of encoding a protein that has anti-tumor activity.

2. (Amended) [An] The adenoviral vector as described in claim 1 or 15 wherein said deletion of said E1b region genes comprises p19, 55K, and pIX genes.

3. [An] The adenoviral vector as described in claim 2 wherein said deletion of said E1b region genes comprises the p19 and 55K genes.

4. [An] The adenoviral vector as described in claim 2 wherein said deletion of said E1b region genes comprises the pIX gene.

5. A recombinant adenoviral vector selected from the group consisting of ΔKmTNF, ΔE1B/CD and Δ55K/CD.

6. (Amended) [An] The recombinant adenoviral vector as described in claim 1 or 15 wherein said heterologous gene encodes a protein selected from the group consisting of tumor necrosis factor alpha, interferon gamma, an interleukin, a cell suicide protein, cytosine deaminase, thymidine kinase and mip-3.

10. A method for directly treating a mammal's [mammal having a] neoplastic condition in a mammal in need of said treatment, comprising administering to said mammal a therapeutically effective dose of said adenoviral vectors of claims 1, 5, 6 or 15.

11. [A] The method as described in claim 10 further comprising administering with said adenoviral vectors a chemotherapeutic or an immunosuppressive agent.

15. A recombinant adenoviral vector comprising a deletion of E1b region gene(s), but retaining the E1b promoter, and substituting for said E1b region gene(s) a heterologous gene that is operable linked to said E1b promoter, and said heterologous gene(s) having the further property of encoding a protein that has anti-tumor activity.